a significant proportion of patients with high-risk hematological disease. This is the first report containing data on long-term toxicity and disease control after any strategy of donor graft manipulation to selectively reduce HLA-mismatched alloreactivity.

39

FEASIBILITY OF UNRELATED UMBILICAL CORD BLOOD TRANSPLANTATION IN CONGENITAL CHILDHOOD DISEASES

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An HLA-matched sibling donor has been the initial choice for children requiring allogeneic hematopoietic cell transplant (HCT). However, less than 30% HCT patients have a matched related donor (MRD). In the past decade, umbilical cord blood (UCB) transplantation has emerged as an attractive alternative for patients without a MRD. Recent studies have shown the advantages of using UCB over bone marrow as an alternative graft source for children with acute leukemias. However, there is less information available regarding the utilization of unrelated UCB transplantation for children with non-malignant diseases. We report the use of an unrelated UCB myeloablative transplantation in fifty-five consecutive children with a median age of 2.6 years (range, 0.2–40.6 years) with Wiskott-Aldrich syndrome, Chediak-Higashi syndrome, hemophagocytic lymphohistiocytosis, langerhans cell histiocytosis, osteopetrosis, Diamond-Blackfan anemia, Hurler syndrome, Maroteaux-Lamy, α-mannosidosis, cerebral X-linked adrenoleukodystrophy, metachromatic leukodystrophy and globoid-cell leukodystrophy transplanted over 11.5 year period (1994–2006). Patients received grafts matched at 6 (14%), at 5 (56%), or at 4 HLA alleles (30%). The median total nucleated cell dose and the median $CD34^+$ cell dose were 5.4×10^7/kg and 4.2×10^5/kg, respectively. The median time to neutrophil recovery was 20 days (range, 10–45 days) and the incidence of neutrophil recovery by day 42 was 86%. The incidence of platelet recovery by 6 months was 73%. In the group of immune or hematological disorders, 6 of 10 patients achieved complete donor chimerism by day 21. In the metabolic disorders group, 8 of 13 patients achieved a complete donor chimerism at a median of 21 days and 3 additional patients at a median day of 95 days. In the leukodystrophy group, 6 of 12 patients achieved completed donor chimerism by day 21 and 4 patients achieved complete donor chimerism at a median of 120.5 days. The incidences of grade II-IV and grade III-IV acute GvHD were 34% and 12%, respectively. Chronic GvHD was observed in only 5% of cases. The overall survival was 62% at 2-years. These results demonstrate the usefulness of unrelated UCB as an alternate stem cell source for patients lacking an HLA matched related or unrelated donor. The use of unrelated UCB transplantation creates new opportunities in the treatment of non-malignant diseases requiring expedient HCT in order to prevent irreversible disease progression.

40

OUTCOMES OF A PROSPECTIVE TRIAL OF NMDP-FACILITATED UNRELATED DONOR (UD) PBSC HEMATOPOIETIC CELL TRANSPLANTATION (HCT) FOR LEUKEMIA AND MYELODYSPLASIA: COMPARABLE SURVIVAL REGARDLESS OF REGIMEN INTENSITY AND IMPROVED SURVIVAL WITH HIGHER CELL DOSES

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We report outcomes of 932 recipients (rcpts) of UD PBSC HCT facilitated by NMDP from 1999 through 2003 (median f/u 3.3 yrs). Indications were AML (419 rcpts), ALL (185 rcpts), CML (134 rcpts), and MDS (194 rcpts). Preparative regimens included myeloablative (MA, N = 611), reduced intensity (RI, N = 160), and non-myeloablative (NMA, N = 161). Distributions of HLA-match grade, CMV status, Karnofsky scores (KS), and donor characteristics were similar between the preparative regimens, however, fewer rcpts with advanced disease received NMA ($p = 0.035$), while more rcpts with coexisting diseases received RI and NMA regimens ($p < 0.001$). The age of rcpts receiving RI and NMA regimens was substantially higher than rcpts receiving MA regimens (median RI 56 yo, NMA 57 yo, MA 38 yo, $p < 0.001$). Optimal cell dose cutpoints for TNC, MNC and CD34+ were determined based on Martingale residuals from Cox regression analyses. For MA rcpts, CD34+ counts $>3.8 \times 10^6$/kg improved day +25 neutrophil and day +60 platelet engraftment; higher infused TNC doses ($>6.9 \times 10^8$/kg) predicted decreased grade III-IV aGVHD, while improved overall survival (OS) and reduced TRM (RR 0.55) were seen with MNC doses $>4.4 \times 10^8$/kg. For RI and NMA rcpts, OS was higher and TRM was decreased in those receiving $>3.8 \times 10^6$ CD34+cells/kg. Of note, cGVHD was not increased with higher cell doses in rcpts of any type of preparative regimen. Additional predictors of improved OS included early disease, and for MA rcpts only, HLA-matched donors, KS ≥ 90, and CsA-based GVHD prophylaxis. Three year OS and DFS of rcpts receiving MA, RI, and NMA approaches were similar (33, 35, and 32% OS; 33, 30, and 29% DFS: MA, RI, and NMA, respectively). Higher risk of relapse at 3 yrs in RI and NMA approaches (35, 37 vs. 24% RI, NMA, MA, respectively, $p < 0.001$) was offset by higher 3 yr TRM using MA regimens (43 vs. 34, 34% MA, RI, NMA, respectively, $p = 0.008$). Sub-analyses of 1) rcpts with AML-CR1, 2) rcpts with AML/MDS/CML (excluding ALL), or 3) rcpts between the ages of 40–60 with AML/MDS also showed similar survival with MA vs. RI vs. NMA approaches. In summary, rcpts of UD PBSC HCT receiving preparative regimens differing in intensity experienced similar survival. Higher cell doses resulted in more rapid engraftment, less severe aGVHD (MA rcpts), and better 3 year OS (37 vs. 18%, MA; 36 vs. 21% RI/NMA, $p < 0.001$), but did not increase the risk of cGVHD.

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41

PRE-TRANSPLANT ADMINISTRATION OF KERATINOCYTE GROWTH FACTOR AFFECTS PERIPHERAL T-CELL HOMEOSTASIS THROUGH INCREASED RECENT THYMIC EMIGRANT EXPORT AND AFFECTS THE COURSE OF MURINE CHRONIC GRAFT-VS.-HOST DISEASE

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Accelerated recovery of thymic function following allogeneic hematopoietic stem cell transplantation (allo-HSCT) not only provides a sufficiently broad repertoire of T-cell responses to pathogens, but also is thought to play a role in affecting the outcome of graft-vs.-host disease (GVHD) through the restoration of central tolerance and/or the production of regulatory cell populations that may blunt the effect of donor-derived alloreactive T-cell populations. Keratinocyte growth factor (KGF) has been shown in murine models to accelerate thymic function and ameliorate acute GVHD, but it is unclear whether the latter involves a thymic-dependent mechanism of increased T-cell production and/or cytoprotection of epithelial cells in target organs of GVHD. We examined the effect of pre-transplant administration of KGF in the B10.D2 into BALB/c murine model of chronic GVHD (cGVHD). KGF treated mice had significantly increased thymic function as assessed by enumeration of thymocyte populations, analysis of thymic cytoarchitecture, and enumeration of peripheral T-cell subsets and recent thymic emigrants (RTE). Significantly, enhanced export of RTE by KGF decreased peripheral T-cell homeostatic expansion and downregulated expression of activation markers, suggesting that RTE effectively compete with post-thymic T-cells for limited cytokines and contact-dependent niches post-allo-HSCT. Parallel experiments in thymectomized recipients receiving KGF exhibited no changes in cell cycle profiles or activation profiles of peripheral T-cells. Pre-transplant KGF administration improved clinical cGVHD outcomes in both thymus-intact and thymectomized recipients. However, there were no observable differences in the course of cGVHD between KGF treated thymus intact and thymectomized mice, suggesting that enhanced thymic function by KGF did not provide for any additional benefit to the cytoprotective effects of KGF. One contributing factor for this observation was